EXHIBIT 7

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the risk of chronic diarrhea?
A. Because you're asking about either paper, why don't I deal with them one at a time?
Q. That is fine.
A. The Lagana paper was interested in abdominal pain, and chronic diarrhea was not the subject of that paper.
Q. Okay.
A. So while it did not have a finding, it also didn't have a question in that regard.
Q. All right.
A. As for the Greywoode paper, we did examine diarrhea. Can you repeat the question about diarrhea?
Q. Right. Did it show an association between olmesartan use and the risk of chronic diarrhea?
A. We did not find that olmesartan was statistically associated with chronic diarrhea. In that analysis of only about 102 or 103 patients who

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take olmesartan, I believe I touched on this earlier, but just to clarify, this was a case-control study that we designed during the early phases of our understanding of olmesartan enteropathy and we wanted to know to what degree the current, or at the time, description of that clinical phenotype represented the tip of an iceberg.
And so we know that we endoscope people for chronic diarrhea. What we didn't know is whether olmesartan is a common cause and the huge underlying cause. We were -- I would say, in retrospect, we were swinging for the fences. We were looking for a really large effect, once we found that olmesartan was not terribly common among patients who come to our endoscopy suite.
That said, when one designs a study and receives data, does analysis, and we find that there are far fewer users of olmesartan in either arm, case or control, than we initially intended,

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one has a choice. One could shove the data in a drawer and it never sees the light of day because it was not statistically significant; and, indeed, there are referees out there and reviewers out there who have indicated that if I see a paper like this, I wouldn't accept it.
Our group generally opts for another choice, which is to come to terms with what we found and even if this results in an answer that's not definitively yes or no, we get it out there, because it's my belief that if we -- if we publish data that we analyze, that serves science, but also gets the word out regarding this condition.
Q. With regard to the criterion consistency in your report, you say, "see adverse event reports and case series below," and those AERs and case series are later discussed in your paper.
Do you see that?
MR. SLATER: What page are

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you on?
THE WITNESS: What page?
MR. MURPHY: 28.
THE WITNESS: I see that.
BY MR. MURPHY:
Q. So you rely on certain adverse event reports and case series with regard to satisfaction of the consistency criterion of Bradford Hill. Right?
A. This is an important piece of the consistency criteria in Bradford Hill that there is a clinical phenotype that's frequently observed. It doesn't mean there's not a spectrum, but that there are some common themes.
Q. And with regard to consistency, AERs and certain case reports are what you rely upon in satisfying that criterion; correct?
MR. SLATER: Objection. That's a mischaracterization of what he just said. You asked him the question, and he answered it.

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THE WITNESS: I look carefully at AERs and case reports because in general, in epidemiological research, even though some people like to put up a generic pyramid in terms of quality of research publications, in truth, often there's a trade-off between quality and quantity.

And so, for example, one could derive helpful information from claims-based data that one cannot get from case reports or case series, but the opposite is also true, because often we can get a convincing narrative regarding the degree of symptomatology and dechallenge and rechallenge data that we can get from a case report or case series that we would not be able to glean from a population-based or large cohort study.

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So it really is about taking all of these into account and acknowledging the limitations of each study type, but not minimizing the strengths either.

BY MR. MURPHY:

Q. And with regard to the case series that you looked at and you discuss in your paper, some of them report 100 response to immunosuppression; correct? For example, DeGaetani --

A. When you say 100 response, do you mean 100 percent response?

Q. Correct.

A. I would take issue with that characterization, because while all of them, all 16 out of 16 olmesartan users, had a clinical improvement, one, that's not the same thing as saying a 100 percent response and, two, they all relapsed after immunosuppression.

Years later, I think most patients and their doctors would disagree that they had a 100 percent response to

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prednisone or budesonide or whatever it was. If anything, it was a transient response, because after all, they all relapsed after, so I certainly wouldn't characterize that as 100 response or 100 percent response.

Q. But majority; correct?

A. I think --

Q. You would agree with majority.

A. I think it's the same issue, that all of these patients had some degree of response, but it's not clear that they had a large response. It just -- it just characterizes that they had a clinical response, which in and of itself, by the way, is somewhat subjective. It depends a little bit on what parameter one's measuring, on what the patient's reporting, and when he or she is reporting it.

And it's very possible for two groups of investigators to be encountering the same emerging clinical

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condition, but to characterize either the presence or absence of a response or the degree of response somewhat differently and particularly in the absence of some sort of disease assessment score.

Q. Was there a response noted to immunosuppression in the Rubio-Tapia paper?

A. When you refer to the Rubio-Tapia paper --

Q. 2012.

A. Okay. Just wanted to make sure we're on the same page.

Their inclusion criterion seem to preclude much of a response. For example, if you look on page 733, they actually excluded a patient from their series because they improved clinically and histologically with oral budesonide before suspension of olmesartan.

That kind of patient might have made it into our series depending on the ultimate outcome with regard to whether that response was durable,

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whether symptoms returned after discontinuation of budesonide, which is an immunosuppressant, and ultimately what happened to that patient once the olmesartan connection was discovered.

So I think that these patients are of a somewhat different denominator simply because of different inclusion criteria.

Q. Right. The fact was, the inclusion criteria, per se, dictated that immunosuppression did not work.

A. These investigators chose to characterize a group with olmesartan-associated enteropathy and by definition they chose to report on what happened to those patients who did not initially get better with immunosuppression.

It appears that later on, they publish further clinical data about some other patients who either did not get all better or much better after cessation of olmesartan or had a more

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variable response to immunosuppression.

Q. So there was a difference in outcome in the different groups with regard to immunosuppression; correct?

A. There was a difference in inclusion. These are apples and oranges. These patients in Rubio-Tapia by definition didn't get better with corticosteroids. They may have had others who did get better, but didn't include that in their initial case series.

We were more inclusive and considered that any improvement, any improvement, with immunosuppression would not be an exclusion criteria. Indeed, as I pointed out, this series that we published was not designed to look for olmesartan. It happens to be that that was described while we were analyzing the data and then lo and behold we found that the lion's share of drug-induced villous atrophy was due to olmesartan.

We set out to do this paper

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in a very different manner compared to Rubio-Tapia and colleagues who specifically, apriori, said we want to look at those patients who aren't getting better, who perhaps some had been previously diagnosed and treated unsuccessfully with celiac disease, and even those on steroids, they didn't get better; if we had patients who did get somewhat better, we're not going to include them for this initial case series.

The DeGaetani paper have a very different set of inclusion criteria, and so it doesn't make sense to compare outcomes with regard to immunosuppression when you're stacking the deck in advance with regard to how they did with immunosuppression at the outset on the Rubio-Tapia paper.

Q. But the fact remains that there were those who had been exposed to olmesartan, had been exposed to immunosuppressants, and did not have a

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response. There was such a group of people. And then there was another group of people who had been exposed to olmesartan, had then been given immunosuppressants, and they did have a response, two different groups of people; correct?

A. Which papers are you talking about?

Q. I'm talking about two groups of people.

MR. SLATER: Objection.

MR. MURPHY: If you cannot answer my question, that's fine.

THE WITNESS: What's the question?

MR. MURPHY: Do you want to read the question back, please?

- - -

(The court reporter read the pertinent part of the record.)

- - -

MR. SLATER: Objection; lack of foundation, ambiguity.

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You can answer.
THE WITNESS: I would put forth that it's not coherent to mix two series together and assume that their definition of response to immunosuppression's the same. As I mentioned earlier, response can be subjective both in terms of durability, temporality, and also strength of response.
And so to say that these are two separate clinical phenotypes that are lopsided in one -- in terms of where they're being distributed with regard to which center they're going to does not make sense. One has to be cautious when looking at terms like response.
MR. MURPHY: Okay.
BY MR. MURPHY:
Q. With regard to the specificity factor or criterion -- and again I'm on page 28 of your report --

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A. I see. Thank you.
Q. -- you cite Basson as a paper that provides evidence to satisfy that criterion; correct?
A. I do cite that. I would also say that the fact that the case reports have been torrential coming in regarding olmesartan and have been so sparse with regard to angiotensin receptor blockers other than olmesartan further lends the notion that there is something about olmesartan that's different with regard to its -- its propensity to cause enteropathy.
It's harder to cite the lack of case reports when writing something up, but I think that that silence is somewhat deafening.
Q. Sprue-like enteropathy is a condition that is caused by things other than medicine and drugs; correct?
A. The words "sprue-like enteropathy" these days generally are followed by "olmesartan" either right

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before or right after; but if you're referring to villous atrophy and if you're going to use those two terms interchangeably, then, yes, villous atrophy can be caused by things other than drugs.
Q. So I'll take another pass at this. With regard to the condition or the phenomenon sprue-like enteropathy, what are its features?
A. What are the features of sprue-like enteropathy related to olmesartan?
Q. Which you say is related to olmesartan. As I understand you, Doctor -- and I want to make sure that you appreciate my question -- sprue-like enteropathy in your mind these days is caused by olmesartan; correct?
A. Olmesartan enteropathy is a known clinical entity. That is not the same thing as saying that all villous atrophy is due to olmesartan. That would be foolish.

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But this condition that's been variously termed sprue-like enteropathy associated with olmesartan, olmesartan enteropathy, olmesartan-induced enteropathy, yes, I believe that is caused by olmesartan.
Were you asking about clinical features?
Q. Yes.
A. I believe I answered earlier in the day that there are a number of both signs and symptoms across a spectrum of several different axes, including clinical, histopathological, and other signs in terms of laboratory abnormalities.
There's no one uniform set of strict criteria that's been developed and there does appear to be a spectrum of abnormalities on all of these axes.
How are we doing on time?
Q. You're fine.
MR. SLATER: Do you want to take a break?

THE WITNESS: Yeah, maybe less than a five-minute break.

MR. MURPHY: Sure.

MR. SLATER: Sure, stretch your legs.

(A recess was taken from 3:32 p.m. to 3:41 p.m.)

BY MR. MURPHY:

Q. Doctor, let me take your attention back to page 28 and your reference to the Bradford Hill criteria in your report.

With regard to the factor or criterion biological plausibility, you cite the Marietta paper "Immunopathogenesis of olmesartan-associated enteropathy"; correct?

A. I do cite that, though I should say this is not exhaustive. First of all, in terms of other criteria I don't list here, cessation of exposure, for example, and there's abundant dechallenge data; but specifically

regarding the criterion of biological plausibility, I mention "(see above under Medical Literature)" and that's relevant.

The Marietta paper is also relevant, but I believe that the link between these symptoms and this clinical phenotype and olmesartan can be explained by certain histological findings that have been identified, just like the link between gluten and feeling ill has biological plausibility, namely villous atrophy and other histologic findings, among others.

Q. With regard to the Marietta paper that you cite here, if you want to go to it, we can --

A. If you're going to be asking me about it, I should take a look. Do you have questions?

MR. MURPHY: Let's mark it.

- - -

(Deposition Exhibit No. Lebwohl-10, 2015 Paper "Immunopathogenesis of

olmesartan-associated enteropathy" by Marietta, et al, was marked for identification.)

- - -

BY MR. MURPHY:

Q. Doctor, you have in front of you what's been marked as Exhibit 10. That's the Marietta paper that you reference in your report in connection with biological plausibility; correct?

A. Among other evidence for biological plausibility, I do cite that study, yes.

Q. Okay.

Now, do you recall that in this paper, in the Marietta paper in front of you marked as Exhibit 10, that NSAID-induced enteropathy was not ruled out or controlled for?

A. I'm not sure what you mean by "controlled for." I don't see a specific note of NSAIDs as an exclusion criterion. It appears that the specimens that were included in this study were

those who had olmesartan-associated enteropathy as abbreviated as OAE, and so I don't see that they used NSAID enteropathy, which is a very different clinical phenotype and often histologic phenotype compared to olmesartan enteropathy, but I don't see specific references to NSAIDs.

Q. And my question to you is, do you know whether the patients for whom these biopsies were taken had been on NSAIDs?

A. I know that in their inclusion criteria, they note that an alternate cause for the enteropathy could not be established after a systematic diagnostic investigation that included investigation for disorders associated with nonresponsive celiac disease as previously reported.

That kind of workup typically involves examination of one's medical history that include medication, whether specified or not specified

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explicitly.
Q. In this study, olmesartan was compared to another -- at least one other ARB; correct? And when I say ARB, I mean angiotensin receptor blocker.
A. Among the different comparisons that were done.
Q. That was one of the comparisons that was done; correct?
A. There were -- there were comparisons to a non-olmesartan ARB.
Q. And with regard to the dosage of olmesartan versus the non-olmesartan ARB, do you know whether there was bioequivalence established?
A. If you mean whether the concentration of these two medications in vitro was the same in their experiments, I do not see that they were calculated to be the same, if that's what you're asking.
What these investigators wanted to know is, when you're bathing the -- these tissue with these agents,

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are you seeing differences, did they go ahead to make sure that these would be identical in terms of their concentrations.
It doesn't appear that to be the case.
Q. Okay. And that is my question.
A. But I would add that what they really want to know is, is there in vitro activity with regard to some immune activation.
Now, the amount of olmesartan or the not-olmesartan ARB that's actually present at the enterocyte level can be extremely variable in human beings simply because of variable rates of dissolving and absorption.
But, no, I don't think that these investigators made sure that these were identical concentrations in their experiments.
Q. Would it not be important to ensure that the concentrations were equal

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to the extent there is comparison between these two agents?
A. I think that the concentration of any drug at the enterocyte level can be so variable between individuals that whether the concentration of these two drugs are identical is not essential.
I would say that if I were in an ideal world and wanted everything to be equal, I would want the concentrations to be the same and I'd want all rechallenges to be controlled in an experimental setting. But that's not the world that we live in, and so it appears that they did what they had available.
Q. Earlier in your testimony, you made reference to the cell line Caco cells.
A. Yeah, Caco or Caco-2.
Q. Caco-2 cells.
A. Yeah.
Q. And in this paper, the

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authors discuss that it was that cell line that they were utilizing for purposes of their study; correct?
A. Among their varied experiments, Caco-2 cells were utilized in this study.
Q. And Caco-2 cells are cells that are found in the large intestine; correct?
A. My understanding is that Caco-2 are derived from a colonic or specifically colon cancer derivation and has been studied extensively in understanding physiology and pathology of the small and large bowel, somewhat akin to HeLa cells, in case you're familiar with that, which are cervical cancer-derived cells, which are of course used ubiquitously in basic science experiments well beyond cervical cancer, but have been found to have helpful applicability to other diseases.
Q. And just so that we're clear, your view is, the fact that these

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cells are from -- or are colonic, are from the large intestine, does not have any impact on the analysis of small intestine enteropathy.

A. I'd say that Caco-2 cells have been studied extensively in the context of small intestinal diseases. It's widely accepted. There's good literature on this. And so, no, it does not strike me as having a red flag.

MR. MURPHY: I want to mark the next exhibit, Greywoode.

- - -

(Deposition Exhibit No. Lebwohl-11, 2014 Paper "Olmesartan, Other Antihypertensives, and Chronic Diarrhea Among Patients Undergoing Endoscopic Procedures: A Case-Control Study" by Greywoode, was marked for identification.)

- - -

BY MR. MURPHY:

Q. Doctor, you have in front of

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you Exhibit 11 to your deposition, which is the Greywoode article, in which you participated with Dr. Braunstein and Dr. Green and others; correct?

A. That's correct.

Q. We talked about this -- this article earlier just a bit, but, number one, I wanted to mark it and make sure it's in the record of your deposition.

My first question is, in this paper describing your study, you all were seeking to determine whether olmesartan use was more common among patients noting diarrhea as a reason for their EGD or colonoscopy as compared to controls who want -- who underwent neither.

A. No.

Q. No?

A. So everyone underwent an EGD or a colonoscopy.

Q. Okay.

A. The question was why were they having the EGD or colonoscopy. Some

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people have it done for a screening colonoscopy, when we turn 50, that's our fate, is that we get screened for colon cancer typically with a colonoscopy.

People have EGDs in this country not just as a screening. Typically, there's an issue and, in some people, that's diarrhea. In some people, it's something else.

So we used this setting, our endoscopy suite, but for a pragmatic reason. It turns out that we capture outpatient medication use pretty well and accurately in our endoscopy suite, because outpatients have preprocedure interviews, and so we thought that would be a good time to figure out -- or setting to figure out -- if there's any association that we have the power to pick up between diarrhea and olmesartan.

So both cases and controls underwent EGD and/or colonoscopy. The issue is, why were they having it done. And cases were having it done for

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evaluation of diarrhea. One can have an EGD for evaluation of diarrhea. One can have a colonoscopy for evaluation of diarrhea. So we chose those as our cases.

And then controls, because of the makeup of the study, we thought that in colonoscopy patients, screening would be appropriate. We don't think they have diarrhea, as far as we can tell, based on the indication field of the endoscopy report.

Now, because there's no screening EGD, we picked another kind of control, and so a common reason people have an EGD that's not diarrhea is reflux, acid reflux -- a lot of people have it -- to evaluate acid reflux.

So those were our controls, but everyone had one of these procedures. I hope that clarifies.

Q. Sure. And the question was, why were they having these procedures?

A. The question was not why are

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we having these procedures. The classification was why are we having these procedures in terms of whether you were a case or a control.

Q. And the case were the folks who were taking olmesartan.

A. No. Case-control studies are that you start with the definition of the outcome. The cases were those who were having diarrhea.

Now, it might be helpful to go over the difference between case-control studies and cohort studies. In cohort studies, the exposed are those who are having the olmesartan and the unexposed are not having olmesartan and then the outcomes, diarrhea, malabsorption, celiac disease, what have you, depending on the design of the study.

In the case-control study, you start with the outcome, and so the cases are those who have the outcome and in this case it was diarrhea and an

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outpatient, and the controls were they're here for some other reason, screening and reflux.

What we were interested in measuring was the exposure and whether olmesartan was more common in one group or another among these patients. We had no idea how common olmesartan use was in this population.

Q. I appreciate that. But your conclusion is set forth in the first page of the article, page 1239; correct?

A. The conclusion of the abstract section?

Q. Yes.

A. I'm there.

Q. "Our findings suggest that neither olmesartan nor other ARBs were associated with diarrhea among patients undergoing endoscopy," that's what you state; correct?

A. "Were associated with diarrhea among patients undergoing endoscopy" is what we stated, in this

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population at least.

Q. Now, the follow-on sentence, "The spruelike enteropathy recently associated with olmesartan is likely a rare adverse effect and milder presentations are unlikely," my question, Doctor, is, when you refer to -- you and your colleagues refer to -- milder presentations, what do you mean?

A. Well, one hesitates before trying to trumpet the implications of one's study too self-servingly and I don't want to go beyond the scope of what we looked at here.

Are you asking about the rare adverse event or the milder presentations?

Q. My question was focused on the milder presentations.

A. Okay. Well, what I'd say is that we did not pick up a signal in this population of outpatients undergoing diarrhea. That said, there has to be a huge proviso that there are only about

Page 269

105 taking olmesartan in this whole study and we now know that given the relative rarity of olmesartan enteropathy, one cannot rule out an association based on 105 patients taking olmesartan, particularly outpatients.

Q. And when you refer to milder presentations, what are you actually talking about when you refer to, again, milder presentations?

A. So I'm referring to the kind of presentation that would be sufficiently mild so as to have a patient undergo this kind of procedure.

But I would add that we actually didn't know a huge amount about this in terms of what their actual symptoms were. All we knew based on this study was, were they outpatients, why were they having their endoscopy, and what was their age/gender, and what were they taking.

I would also point out, you know, this was published in 2014 and I'm

not sure I would still put forth that milder presentations are unlikely in general. They were not detected in this small study, but the more we learn about the relative uncommon prevalence or incidence of olmesartan enteropathy and the fact that you need a lot more patients to -- on olmesartan to detect something and the fact that there have been a flower in the case reports that put forth more mild presentations, I'm less confident that it's still the case that milder presentations are unlikely.

I was putting forth a hypothesis in the setting of a limited abstract word count where I couldn't put in these provisos that you are kindly letting me put in here.

Q. There was more that you had to say, but you were constrained by page limitation; is that what you're saying?

A. In the world of academia, word count can sometimes limit our ability to express ourselves totally

clearly.

MR. MURPHY: Let's mark as 12 -- I'm going to mark the Lagana paper that you wrote with Dr. Braunstein, Dr. Green, and others.

- - -

(Deposition Exhibit No. Lebwohl-12, 2014 Original Article "Sprue-like histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers" by Lagana, et al, was marked for identification.)

- - -

THE WITNESS: Okay.

BY MR. MURPHY:

Q. Do you have it?

A. Yes.

Q. Now, Dr. Lagana is a pathologist; correct?

A. Yes, he's a pathologist.

Q. And his report, you reviewed; is that -- is he on your

reliance list?

A. I'm just --

MR. SLATER: You told me not to say anything to shorten the time --

THE WITNESS: I'm just glancing at my reliance list to make sure I don't speak inaccurately. Give me a minute to find my reliance list.

MR. SLATER: It's right here. He's your report.

THE WITNESS: Thank you.

MR. SLATER: I helped you. Take a walk around the table twice to just eat up that time I just saved.

THE WITNESS: Yes, it's listed on my reliance list.

BY MR. MURPHY:

Q. His general report.

A. Correct.

Q. In the study that's discussed in the paper in front of you,

you and your colleagues compared 20 olmesartan-exposed patients undergoing duodenal biopsy to a control group of 20 non-ARB users.

A. No, we did not compare the two of those. We compared each group to matched controls.

Q. And was there yet another group?

A. There were four groups total. There was an olmesartan user group. There were the controls matched to olmesartan users. Third, there was another non-olmesartan ARB users group and, fourth, there was a control group matched to those non-olmesartan ARB users.

Q. All right.

And as reported in your abstract on the first page, you concluded that there were no statistically significant differences between olmesartan users with abdominal pain and controls for any single histopathological

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abnormality. Right?
A. We wrote, "No single histopathological finding was significantly more common in olmesartan users than controls," yes.
Q. So what I said is correct?
A. That was an accurate paraphrase of what we wrote.
Q. If I could direct your attention to table 2, among your group of olmesartan users who demonstrated one or more sprue-like feature, there was 10 of 20; correct?
A. In table 2?
Q. Yes, sir. If you look to the bottom --
A. The final row does indicate that 10 of 20 or 50 percent exhibited one or more sprue-like features.
Q. Now, the controls were the folks who were not taking olmesartan; correct?
A. There are two groups of controls.

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Q. Right. Non-olmesartan and non-ARB total --
A. I wouldn't lump them together.
Q. Understood.
A. Each was matched to its own ARB user, so there was a control group matched to the olmesartan users and there was a control group matched to other ARB users.
Q. So just focusing on the olmesartan users, the controls matched to the olmesartan users, 4 out of 20 of those folks reported one or more sprue-like features; correct?
A. Well, those folks didn't report any of these things. These were all blinded observations by an expert pathologist. But, yeah, it was -- these -- one or more features were observed by that pathologist in 4 out of the 20 matched controls.
Q. And then with regard to the group that was taking an ARB other than

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olmesartan, in 9 of the 20, one or more sprue-like features was observed or were observed; correct?
A. 9 out of 20 patients had one or more sprue-like feature observed in that group, but I would be cautious in comparing the olmesartan users directly to the other ARB users because they had some differences, which I believe we characterize in table 1.
Q. And with regard to the matched controls, that is, the folks that were matched to the other ARB users, 12 out of 20 demonstrated one or more sprue-like features; correct?
A. Correct in that if you look at table 2, 12 out of 20 controls matched to the other ARB users exhibited one or more features.
Q. So the largest number of reports of sprue-like features came from a matched control group that was not exposed to olmesartan; correct?
A. Well, I think if one zooms

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out and just looks at raw numbers, one can say the biggest number in that table in parentheses is in that column, but I don't think that that's a sound way to look at this.
We matched controls to users for a reason. If the olmesartan users and the other ARB users differ in terms of baseline characteristics, then it's appropriate to compare the matched control to the appropriate user and not to just look at what's the largest number on that table.
Q. But just so that we are clear, 12 out of 20 folks who had not been exposed to an ARB generally or olmesartan in particular demonstrated one or more sprue-like features; correct?
A. That's what we found.
Q. Okay. That's all I'm asking.
Now I'm going to ask you to go back to your report, specifically page 16.

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A. I'm at page 16.
Q. Okay.
And I'm four lines up from the bottom to the right, the sentence begins, "Of note, we discussed a case report we defined as having 'considerable relevance to our study,' describing a patient who presented with constipation, but not diarrhea, and varied findings on duodenal biopsy" and then you cite to Talbot, T-A-L-B-O-T; correct?
A. I see that.
Q. Now, in the actual statement that I read, you indicate that that patient reported with constipation, not diarrhea; correct?
A. Correct. And, indeed, it says in the research layer, the patient reported no diarrhea, but had occasional mild constipation.
Q. I had earlier asked you about features of olmesartan-associated enteropathy, and my question to you here is whether constipation is among those

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features.
A. It has been reported among patients with evidence of olmesartan enteropathy. I would say that based on what we know today, I believe that diarrhea is more common than constipation, but constipation can be a feature.
Q. Constipation can be a feature. Diarrhea can be a feature; correct?
A. Yes, both could be features of olmesartan enteropathy, though we have more reports and experience with diarrhea as a feature.
Q. How about vomiting?
A. Vomiting has been reported as a feature of olmesartan enteropathy. That is not a necessary feature, but it certainly been reported in adverse event reports or in case reports or case series.
Q. Are there any features that you would characterize as necessary

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features?
A. Yes.
Q. Which of them are necessary?
A. Exposure to olmesartan.
Q. Anything else?
A. I think it's hard to be black and white about a prototypical clinical scenario right now. There appears to be a spectrum, both histologically and clinically.
And so while there are certain features that have been reported commonly in patients with olmesartan enteropathy, like diarrhea, like weight loss, that seems to be particularly common, there are also patients who have neither of those who end up having olmesartan enteropathy. Vomiting is another such example.
But really none of them is absolutely necessary for the development of olmesartan enteropathy.
Q. With regard to this patient that is discussed in the Talbot paper,

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was the patient given or exposed to a gluten-free diet at any point?
A. It says in the research letter that most remarkably, a gluten-free diet -- oh, I'm misspeaking. I'm -- in the beginning of their letter, they're characterizing the Rubio-Tapia paper.
Later on, they do note that a trial of a gluten-free diet was considered, but the patient elected not to pursue this given the absence of symptoms, et cetera.
Q. So there was no gluten-free diet imposed.
A. Not at the time of the description of the case, no. It was suggested or brought up, but the patient had other -- other plans in mind, I suppose.
Q. And with regard to the discontinuation of olmesartan, was there any follow-up to determine what happened or how the patient responded to the

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discontinuation of olmesartan?
A. This research letter is somewhat open-ended with regarding what happened ultimately. I can quote. It says, "Olmesartan therapy will be discontinued with monitoring of Vitamin B-12 levels," et cetera, implying that this is a work in progress.
Q. So it's unclear what happened with this patient --
MR. SLATER: Objection.
You can answer.
BY MR. MURPHY:
Q. -- upon discontinuation of olmesartan; is that right?
A. Based on what's described in this research letter, we don't have long-term data on what happened to that patient.
Q. In your report, that is, your report setting forth your opinion, do you identify all of the case reports, Doctor, where olmesartan rechallenge is described?

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A. Is the question regarding whether I mentioned every single publication or adverse event report that includes a rechallenge?
Q. No. Do you identify those case reports -- do you identify where rechallenge was described?
A. I make reference to rechallenge in the report and if you'd like, I can give you an example.
Q. Sure.
A. In my summary of the Rubio-Tapia 2012 paper, I describe that -- the following: "All patients improved upon dechallenge and deliberate rechallenge was not performed due to the severity of the risk; however, the authors note that a rechallenge occurred in a history of four patients."
I then quote, "No deliberate rechallenge test with olmesartan was undertaken because of the life-threatening nature of the syndrome, although two patients reported

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anecdotally that their symptoms had worsened when they restarted olmesartan before the potential association was recognized, and two patients experienced improvement when olmesartan was stopped when they were hospitalized for dehydration and hypotension and worsened in the weeks following discharge and reintroduction of olmesartan."
Q. So as to Rubio-Tapia, rechallenge was not something that was planned or anticipated. It was, the term that was used, anecdotal.
A. I think the anecdotal has a disparaging implication, frankly, in the discussion of a potentially fatal drug effect. In fact, many case series involved very ill patients who when rechallenged don't do so under controlled circumstances, because no caring physician would -- or -- would offer or no patient who is very ill likely from olmesartan would agree to a so-called controlled rechallenge in many

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circumstances.
Instead, we rely on this kind of story where olmesartan is reintroduced over the course of a drawn-out illness in which patients are off olmesartan because, for example, they're hospitalized and so they get better during that hospitalization, in retrospect clearly due to the olmesartan, or because they're losing so much weight, suddenly their high blood pressure -- or, rather, gradually, their high blood pressure -- is no longer a pressing issue and they're taken off the olmesartan and they get better.
One wouldn't call those controlled, but I'd be hesitant to dismiss them as anecdotal. I think it's quite compelling.
Q. "Anecdotal" was a term that you read. That is where -- the origin of my use of the term "anecdotal."
But my question to you is -- was simply whether the folks -- the

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Rubio-Tapia authors and investigators -- planned, intended to conduct a rechallenge.

A. They are clear that they did -- they deliberately did not do that because of the life-threatening nature of the syndrome.

Q. Understood.

And so then my question to you is, are there any other case reports, other than Rubio-Tapia, that describe a rechallenge?

A. There are other case reports that describe a rechallenge.

Q. Which one or ones?

A. Are you referring to published articles by medical literature or also adverse event reports?

Q. That you discuss in your report.

A. Okay. Would you like me to mention all of them or just one of them or what would you like?

Q. Well, you can just -- you

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can identify one of them and I'll have a follow-up question and we'll see whether your answer applies to all.

A. Marthey and colleagues, the title of the paper is "Olmesartan-associated enteropathy: results of a national survey." That includes reports of rechallenges.

Q. And the rechallenges reported upon by Marthey, et al, do they indicate the duration of the discontinuation period before rechallenge was initiated?

A. Can you repeat the question?

Q. Sure.

Do they indicate the duration of the discontinuation period, that is, the period between discontinuation and reinitiation?

A. They use one illustrative case in a figure that indicates the duration of olmesartan holiday, if that's what you mean.

Q. Yes.

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A. But they also mention that they found other olmesartan rechallenges that they're reporting in this study in which they do not specify the duration of dechallenge period or drug holiday prior to rechallenge.

Q. So with regard to the drug holiday, that one instance of drug holiday that is identified in terms of duration, how long was that drug holiday?

A. So what's illustrated in one case, it appears that in this one patient, there were multiple drug holidays and they each lasted about one month.

Q. One month.

A. In that one case.

Q. And do you know, Doctor, whether a one-month drug holiday is sufficient to allow the changes that were caused by the diarrheal illness to resolve?

A. I know, based on my clinical experience of taking care of patients

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with olmesartan enteropathy, that the clinical improvement can in some cases be quite rapid and dramatic, well -- well less than one month.

Q. So is the answer to my question, your experience is that a one-month holiday is sufficient?

A. Not universally sufficient, but certainly it's compatible with a positive dechallenge and rechallenge.

Q. When you say it's compatible, what do you mean?

A. It's within the realm of patients I've seen certainly and what's been reported in the medical literature.

Q. The last part of what you said, I think I caught it, it's been reported in the medical literature that a one-month holiday is sufficient; is that what you said?

A. It's been reported that a one-month holiday has resulted in resolution of symptoms or improvement of symptoms such as is the case in this

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study that I just referenced. And we're talking about clinical symptoms, not necessarily other abnormalities, whether it be laboratory or histologic.

And, again, analogy's helpful in this regard. So in celiac disease, if you take a patient with severe symptoms who's eating gluten and you diagnose him successfully and you start a gluten-free diet, in the context of appropriately elevated celiac disease serologies, often clinical improvement well predates improvement of histology, which can sometimes take years, or serology, which has, again, a more variable -- a more variable time course with regard to improvement or resolution.

And I've observed a similar clinical variability with olmesartan.

Q. So the clinical manifestation of getting better is not necessarily proof that the histologic changes have occurred.

A. A clinical response does not

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correlate with a histologic response, if that's what you're asking. That's certainly the case in celiac disease.

And I think we have less histologic data upon which we rely on the olmesartan story, but I believe that the situation is analogous, that you can potentially have a difference between how a patient is doing clinically when dechallenged and how they're doing histologically.

Now, the scientist in me wants to know that answer very well and wants to study this more, but as a patient who cares -- as a physician who cares for patients, the patient cares most about clinical response; and when you have a patient in front of you who's so much better off olmesartan, it is not always clinically so relevant to the patient how they are doing histologically.

Q. But to the extent that there is a rechallenge attempted, is it not

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important to determine whether, histologically, there has been repair?

MR. SLATER: Objection.

You can answer.

THE WITNESS: If you're referring to histology after rechallenge, I would not assume that there's repair.

BY MR. MURPHY:

Q. I'll take one step back. We were addressing the drug holiday and whether a one-month drug holiday was sufficient; correct?

MR. SLATER: I'm sorry. We're not talking about a drug holiday in Columbia, are we? All right. That was a bad joke. Go ahead.

THE WITNESS: Can you repeat the question?

MR. MURPHY: Oh, sure.

BY MR. MURPHY:

Q. We were discussing drug holiday and whether a drug holiday of one

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month was sufficient before embarking upon a rechallenge.

A. You'd asked me about duration --

Q. Duration.

A. -- and so forth, yes.

Q. And one of the things that you told me is that you had observed a drug holiday of one month to be sufficient to observe clinical improvement.

A. I've observed that by looking at the literature and, clinically with my patients, I've had patients tell me that they felt markedly improved, even within days. And, indeed, a lot of the rechallenge data we have comes from hospitalizations, which are typically, thankfully, measured in doses of days and not weeks.

And often these are multiple dechallenges, often just for a few days at a time, and yet the patients are off the drug long enough to feel

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significantly better and have a taste of what they ultimately will achieve once it's figured out that it was olmesartan all along and then they're off it for good.

Q. Before a rechallenge can be initiated, there has to be a drug holiday; correct?

MR. SLATER: Objection.

You can answer.

THE WITNESS: I'm not sure what you mean by "there has to be." Now, as I mentioned earlier, people don't take drugs as a continuous drip or infusion. People take drugs or medications on a schedule, and so one is technically off a drug even if they're taking it daily, but that I would not consider to be a holiday.

We need to take into account the half-life. Once one's missing a day or two of drug, if it's

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prescribed daily, that has been reported to result in significant improvement.

BY MR. MURPHY:

Q. I want to make sure we're properly wording this. In the papers that discuss rechallenge, there is a period at which the patient discontinued the olmesartan; correct?

A. That's the definition of a dechallenge.

Q. Right. And what I have been asking you about is the duration of the period of nonuse which we have called the holiday, drug holiday; correct?

A. You've asked me -- I've given you one example of duration; and if you'd like to know other durations, I could try to find some more for you.

Q. It's not the duration. It's just the definition I'm talking about, that period between discontinuation and reinitiation.

A. In this situation, it was

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approximately one month according to the figure.

Q. And so my question to you is whether you know if one month is sufficient to allow the histological changes of the diarrheal illness to resolve.

MR. SLATER: Objection. This has been asked and answered multiple times.

You can answer.

THE WITNESS: I believe there's marked variability in healing rates. I'm primarily relying on extensive experience we have with an analogous enteropathy, namely celiac disease, in terms of gluten and variable rates of intestinal healing that correlate poorly with clinical improvement. We have less data on olmesartan for the reasons I described earlier, but I believe that there's a similar

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variability.

How are we doing? Can we take a brief --

MR. MURPHY: We can take a brief break.

(A recess was taken from 4:34 p.m. to 4:44 p.m.)

BY MR. MURPHY:

Q. Doctor, let me direct you to page 37 of your report.

A. I'm on 37.

Q. At Roman numeral 4, there's the heading "Internal Documents Addressing Olmesartan Enteropathy." Do you see that?

A. I see it.

Q. And your first sentence there reads, "Daiichi Sankyo's internal documents provide foundational information that is helpful in understanding the nature of Olmesartan enteropathy, and the causality."

Did I read that accurately?

A. Correct.

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Q. Now, internal pharma company documents aren't the type of things you rely upon in your practice in making decisions whether to prescribe for your patients, are they?

A. Internal documents are by their definition not something that I'm or anyone typically privy to, and so I don't have the opportunity to rely on those on a day-to-day basis in my clinical practice.

However, given that the clinical entity that's discussed is one that I'm very familiar with, have cared for in terms of my clinical practice, and have published on, I did not find it difficult to review those.

Q. Doctor, are you aware that internal communications among pharmaceutical company employees are not part of or included in filings with the FDA?

MR. SLATER: Objection; lack of foundation.

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BY MR. MURPHY:

Q. Are you aware of that?

MR. SLATER: Objection; lack of foundation, mischaracterization.

THE WITNESS: I think that when one discusses internal documents, this could refer to confidential documents that no one is privy to outside the company, as well as documents that are shared with the FDA, but not the general public.

BY MR. MURPHY:

Q. Have you ever been employed by a pharmaceutical company, Doctor?

A. No.

Q. The internal documents addressing olmesartan enteropathy that you reference here in your report, how did you come to select those documents?

A. Can you specifically point out where in my report we're referring to or in general?

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Q. We're at page 37 and you make the statement that internal documents provide foundational information, right, that is helpful in understanding the nature of olmesartan enteropathy and the causality.

A. Okay. Now I understand the question. I thought that you were asking for a specific document.

I encountered them in the course of my preparation of this report when I was reviewing depositions and documents were included as exhibits, which included, but were not limited to, internal documents, and that's when I reviewed them.

Q. Those were provided to you by counsel; correct?

A. Yes.

Q. Are you aware that in this litigation, Daiichi has produced millions of pages of documents? Are you aware of that?

A. I certainly haven't looked

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at all these pages, but I would imagine that any large company that produces a drug that ultimately is approved generates a lot of paper, maybe -- hopefully not all printed out, but I imagine it's abundant and I wouldn't be surprised if it were in the millions.

Q. And with regard to the company documents that were provided to you as exhibits to depositions and the like, do you think it's important to understand the context in which those documents were created?

A. I think when reviewing any document, it's important to think about when that document was created, who created it, who it was sent to, and what was done in response and so by -- by that, I mean -- I would mean context.

I don't think one has to read the millions of pages in order to have a good context of what these documents are about.

Q. Well, my question was

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specific to reviewing an individual document, and that is whether it's important to have a context for the creation of the document. That was my question.

MR. SLATER: Objection to the form.

You can answer.

THE WITNESS: It's somewhat abstract. What I'd say is, in terms of documents that I was privy to in the course of reviewing depositions, the depositions provided some context and it's also helpful to look at the date of the document and understand where people were in terms of their understanding of what was going on, and so that often provides appropriate context.

BY MR. MURPHY:

Q. Before you were engaged as an expert in this litigation, had you

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ever submitted a MedWatch report?

A. I vaguely recollect, years ago, when I was a trainee, reaching out to the FDA about an adverse effect that I witnessed in a patient of mine. It was not related to olmesartan. And I can't be sure to what extent it was completed.

I certainly never heard back from the FDA, and I remember the process was one that left me with the feeling that these adverse events surely go underreported.

Q. So that we are clear, my question to you about ever having submitted a MedWatch report is not specific to olmesartan. I just want you to understand that.

So am I to understand that the one instance in which you vaguely recall having prepared and submitted a MedWatch report dealt with olmesartan?

A. Oh, it definitely was not about olmesartan.

Q. Ah.

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A. It was about a nutritional supplement that appeared to cause liver damage, and I was very concerned about it and so I remember reaching out to the FDA and being somewhat frustrated with the process.

I felt that, ideally, reporting adverse drug effects shouldn't be onerous and should be easy to do, and that left me with the sense that adverse drug effects are underreported because it's not so easy.

Q. In your practice, Doctor, do you go online and try to view MedWatch reports?

A. I certainly read case reports of adverse drug interactions. Sometimes that's done in the context of collated reports, for example, Micromedex or other frequently used resources that include a mix of published literature and summaries of MedWatch reports. That's one.

There's also a site that's

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NIH sponsored that's specifically tailored towards liver toxicity, and so I'm quite familiar with reading the contents of the report, if not the physical report itself.

Q. And so my question was, with regard to MedWatch reports in particular, do you go online and review them in your clinical practice?

A. In my day-to-day clinical practice, I don't specifically review MedWatch reports in their native form, so to speak; but as I say, there are abstractions of those reports, including in some cases very close reiterations of those reports, that make their way into these other resources cited above. They tend to be more user friendly, handy, and readily available.

Q. So to the extent one or more MedWatch reports may be discussed in a larger article, so to speak, that is the context in which you typically would review a MedWatch report. Fair to say?

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A. So that's right in that I will see encapsulations of MedWatch reports in the context of lists of reports of adverse effects of drugs.

Q. In your clinical practice, do you diagnose or treat your patients' conditions based upon your review of MedWatch reports?

A. When I am diagnosing or treating patients, if the issue of a drug-related effect might come out and rise to the fore in terms of my differential diagnosis, I would use one of those -- one of those resources online, which again are not the MedWatch reports themselves, but may incorporate elements from them.

So indirectly, yes; directly, less so.

Q. Doctor, I'm going to ask you to turn to page 32 of your report.

A. Okay. I'm on page 32.

Q. And starting at the bottom, you make reference to a number of

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MedWatch reports and the testimony that certain company witnesses gave relative to those, and I'm going to ask you a couple questions about those MedWatch reports. Okay?

A. Okay.

- - -

(Deposition Exhibit No. Lebwohl-13, 10/10/15 MedWatch Report (Also Marked as Exhibit 749), OLM-DSI-0004775145-R and OLM-DSI-0004775146-R, was marked for identification.)

- - -

BY MR. MURPHY:

Q. So, Doctor, you have in front of you Exhibit 13, and Exhibit 13 is a MedWatch report that is the subject of your discussion at page 32 regarding Tina Ho.

A. I see that there's a MedWatch report referenced on the bottom of page 32. I don't see that a report number is made reference to in that

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report in that section and so I can't confirm that this report corresponds to that report number.

Q. And so if you look at Exhibit 13, it has an exhibit number from Tina Ho's deposition; correct?

A. It says 749.

Q. Correct.

MR. SLATER: I'll agree that this is Exhibit 749.

MR. MURPHY: From Tina Ho's deposition?

MR. SLATER: From Tina Ho's deposition. I was really close by when that happened.

MR. MURPHY: I got that sense.

BY MR. MURPHY:

Q. So just so that we are clear, Doctor, what Mr. Slater is saying is that Exhibit 13 in your hand is the MedWatch report about which Tina Ho was questioned as reflected in your report.

A. On the bottom of page 32.

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Because I believe Tina Ho was questioned about more than one MedWatch report to the best of my recollection. I just want to make sure I'm not misspeaking, that this is the right MedWatch report for this specific scenario.

Q. Correct. That's the one.

MR. SLATER: Right. From 32 over to 33.

THE WITNESS: Thank you. Just being careful.

MR. SLATER: No, you should be. It's a lot of paper.

BY MR. MURPHY:

Q. Now, with regard to this MedWatch report, just a couple questions: Do you see that this patient reported abdominal pain two months after beginning olmesartan?

MR. SLATER: Objection; incomplete.

THE WITNESS: Well, let's see. So this event date is specified as March of 2006. A

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date within March isn't specified, so -- but they mention March 2006. The report was generated in 2015.

Of note, 2006, the date of the event, well predated widespread dissemination or really any dissemination of olmesartan enteropathy --

MR. MURPHY: Doctor, do you remember my question?

MR. SLATER: Yeah, you can quietly read and then answer his question, just so --

THE WITNESS: I believe you were asking about symptoms in this patient.

MR. MURPHY: I asked you whether the document indicates that the patient reported pain after two months of olmesartan therapy.

(Pause.)

THE WITNESS: On the second side of the report, it notes that

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the patient suffered abdominal pain in March of 2006 under therapy with Olmetec R, 20 milligrams a day, that was started two months before -- before, period.

And so if that's what you're referring to, that's what's mentioned there --

BY MR. MURPHY:

Q. Given what you read, does that indicate to you that the patient reported abdominal pain two months after having started olmesartan therapy?

A. Well, there's more that's reported in this document.

Q. With respect to the question I just asked you?

A. It's very possible that this patient had --

MR. SLATER: I'm sorry. Before you -- can I hear the question read back? I'm sorry. I looked at an e-mail.

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MR. MURPHY: Sure.

MR. SLATER: Yeah, I know. I totally lost it.

Can you just reorient me, Kim?

- - -

(The court reporter read the pertinent part of the record.)

- - -

THE WITNESS: I would say that abdominal pain, I clearly see documented two months after treatment with olmesartan, but --

MR. MURPHY: Okay.

THE WITNESS: -- diarrhea and vomiting began one month after treatment of olmesartan. We can see that on the first page of the MedWatch document.

It's possible that this patient also had abdominal pain at that point because it's very common for someone who's having diarrhea and someone who's having

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vomiting, particularly if it's severe enough to have concomitant abdominal pain.

But the specific question of abdominal pain in terms of temporality, it appears that two months is when it's first documented in this summary.

BY MR. MURPHY:

Q. Focusing on the diarrhea -- diarrhea within one month after starting olmesartan therapy, that is inconsistent with the onset of symptoms reported by Rubio-Tapia in their 2012 paper; correct?

MR. SLATER: Objection. You can answer.

THE WITNESS: The range reported by Rubio-Tapia was .5 years to 7 years, and so the soonest they were able to -- or the earliest report that they had, at least that fit the inclusion criteria that we talked about earlier, was six months and so

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this does fall out of the range of the initial case series.
MR. MURPHY: Okay.
BY MR. MURPHY:
Q. Now, there was abdominal pain followed by diarrhea. We've read that in this MedWatch report; correct?
MR. SLATER: Objection; incomplete.
You can answer.
THE WITNESS: Abdominal pain was noted two months after starting olmesartan. Diarrhea and vomiting was noted one month after starting olmesartan, so I'm not sure it's accurate that there was abdominal pain followed by vomiting, diarrhea. It could be that it was actually the reverse if we were to take this report literally.
It's also possible that they were all swirling around together, which is frequently what happens

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when patients have GI upset, that the exact temporality of which of these GI upset symptoms happened first, some patients recall it pristinely; others, it's just a generalized GI upset and they all sort of happen together.
BY MR. MURPHY:
Q. Those two symptoms, diarrhea and abdominal pain, occurring within two months after initiation of olmesartan therapy, that alone, is that sufficient to make a diagnosis of sprue-like enteropathy caused by olmesartan?
A. Well, one doesn't like to take symptoms in a vacuum. Certainly that along with the rest of this report review was enough to lead the manufacturer to assess that the causal relationship between drug and this event was definite.
Q. The assessments made by the manufacturer were not done pursuant to a full case workup, are they?

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A. Is that a question?
Q. Yes.
A. Can you define "pursuant to a fuel case workup"?
Q. Sure. When you endeavor to determine the cause of your patient's enteropathy, you do a workup; correct? Or you engage in a differential diagnosis; correct?
A. I engage in a differential diagnosis.
Q. And so the causation assessment made by the company, as you term it, was not done pursuant to a differential diagnosis, was it?
A. I disagree. One can generate a differential diagnosis when reviewing data even without having that patient across the desk from you or on the examining table. One makes one's impression based on the available data.
In some cases, there's a wealth of data and you can go back and talk to the patient. In others, there's

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more limited data or circumscribed data, but the process of formulating a differential diagnosis and then concluding the probability that there was a causal relationship, that's a similar process. It's just that the inputs may vary.
Q. Is it your understanding, Doctor, that the MedWatch reports that you've seen in this litigation were -- that is, the causation assessments made in those MedWatch reports -- were done pursuant to a differential diagnosis?
A. They were done pursuant to the available data that was there at the time. Now, a differential diagnosis is a process that's very commonly employed when attempting to assess for causality because one has to keep in mind what the alternatives are.
Now, if someone had reviewed this and said, you know, I think the alternative is X, Y, or Z, they would not be characterizing the causal relationship

between a suspected drug and the event as definite, because implicitly, a differential diagnosis suggests an alternative as a more plausible cause.

Q. In this MedWatch report that we're looking at here, Exhibit 13, is there any mention or evidence of a biopsy having been taken?

(Pause.)

THE WITNESS: Based on what's written in this MedWatch report, I do not see a report of a biopsy having been performed.

MR. SLATER: We gotta take a break for about three minutes. I just got an e-mail. I gotta call someone back. This will probably be maybe our last break before he finishes, but I gotta take three minutes.

THE WITNESS: All right.

(A recess was taken from 5:09 p.m. to 5:14 p.m.)

BY MR. MURPHY:

Q. Doctor, directing your attention to page 33 of your report --

A. I'm on page 33.

Q. -- and the first full paragraph, you identify a MedWatch report and you say it's reported to Daiichi-Sankyo on March 22nd, 2007.

Do you see that?

A. I see that.

Q. And then you go on to say that it discusses a patient with reported massive diarrhea, severe dehydration, and a 20-pound weight loss; correct?

A. I do mention that in the report.

Q. And then you then state, "There is positive dechallenge and positive rechallenge as the symptoms abated when the medication was stopped, and the symptoms recurred when the medication was restarted."

A. Give me a moment. I lost track of where you were reading from.

Here, I have it. I see it.

- - -

(Deposition Exhibit No. Lebwohl-14, 10/11/15 MedWatch Report (Also Marked as Exhibit 347), OLM-DSI-0004774183-R and OLM-DSI-0004774184-R, was marked for identification.)

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BY MR. MURPHY:

Q. Doctor, I'm handing you what's been marked as Exhibit 14 to your deposition. And if you take a look at the top-right aspect of the document, you will see the MedWatch number that you reference in your report.

A. I see it, yes.

Q. So with regard to this patient, as you had stated, the MedWatch report in the description of event or problem states at least in part, massive diarrhea, a weight loss of 20 pounds, and severe dehydration while taking Benicar. It's in the first page in box number 5.

Do you see that?

A. I'm looking now. Give me a moment, please.

Q. Uh-hum.

(Pause.)

BY MR. MURPHY:

Q. So my question was --

MR. SLATER: Hang on. He's still reading.

THE WITNESS: I'm almost done --

MR. SLATER: I want him to take the time to actually read the document to prepare for the question.

(Pause.)

THE WITNESS: Okay.

BY MR. MURPHY:

Q. And having read the entire document, you see where there's follow-up information provided by the patient's doctor; correct? The back side of where you were reading.

A. Are you referring to the additional information received on March

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22nd, 2007?
Q. Correct.
A. I see that section.
Q. Right.
And it reads at least in part, according to the physician, the patient has never experienced similar events; and then the next sentence, the physician also reported the patient has a history of atrial fibrillation for which he takes Rythmol SR, 325 milligrams, twice daily.
Do you see that?
A. I do.
Q. Are you familiar with the common side effects associated with that medicine?
A. If you're referring to propafenone --
Q. No, I'm referring -- yeah, exactly, propafenone.
A. Offhand, I can't list a list of the most common, but it would not be unexpected for it to have the typical

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list of side effects that many drugs are associated with in -- when measured in their phase three studies, but offhand, I can tell you that it has not been shown to be associated with or to cause enteropathy.
This is a medication that I am familiar with and it is not one of the medications that have been -- that have been jumping out in my clinical experience.
I'd also point out that despite the fact that propafenone is in the picture and the patient does take propafenone, Allen Feldman, who was the vice president of pharmacovigilance at Daiichi, testified that in this case, the only plausible case of this patient's illness was olmesartan. And I agree with that assessment.
MR. SLATER: Just for the record, you said "case of." You mean "cause of."
THE WITNESS: Correct. The

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only plausible cause of this patient's illness was olmesartan.
BY MR. MURPHY:
Q. And with regard to the testimony you attribute to Dr. Feldman, Dr. Feldman was testifying to what was, in fact, reflected in this MedWatch form, correct, as being the only thing that one could rely upon to make a determination?
A. I believe that those were the data that he was looking at at the time of that assessment.
Q. Right.
Now, going back to the side effects, the common side effects, associated with propafenone, are you aware that nausea, vomiting, and constipation are reported as common side effects?
MR. SLATER: Objection.
You can answer.
THE WITNESS: I'm not at all surprised to hear it. In fact, if you were to take many prescription

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drug medications, if you look at common side effects, for example, in a Physicians' Desk Reference or in Epocrates, you'll find nausea, vomiting, diarrhea. That in and of itself is a far cry from the kind of clinical phenotype that we observed with olmesartan.
BY MR. MURPHY:
Q. You reference --
A. I also --
Q. I'm sorry. Go ahead.
A. I also don't see any indication that the Rythmol, otherwise known as propafenone, was adjusted or changed during the course of his illness; and if you have a medication that has as a somewhat generic side effect these GI disturbances and then you have olmesartan which has been implicated in sprue-like enteropathy and you change one and not the other, and the patient gets better and you have rechallenge data, which is evinced here -- if you look on the first

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page, the diarrhea returned when the Benicar was continued, and that's also coded here in box number 8, the diarrhea appeared after reintroduction -- I don't think it's plausible and I don't think it would pass the laugh test if one were to say, well, the -- it was actually the propafenone that is a plausible alternative cause of his problems when, in fact, we don't have that kind of dechallenge or rechallenge history.

And I think it would be unlikely that both medicines would be started and stopped at the same time.

Q. So that was a question that I was going to ask you. With regard to discontinuation of olmesartan, do you know whether the propafenone was discontinued at the same time? It doesn't indicate, does it?

A. It doesn't say that it was discontinued. It says that he takes propafenone, and so my understanding is that he continued to take that.

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After all, as you likely know, it's an antiarrhythmic and especially when someone's acutely ill, stopping the antiarrhythmic is not something that's generally done. Particularly if one's atrial fibrillation is intermittent, times of stress can worsen atrial fibrillation.

So while it's not explicitly pointed out here, in every MedWatch report you're never going to get the entire story. There are going to be situations where if you had the patient in front of you, you might for various reasons ask for clarifications, but I have no indication here that it would be plausible that the propafenone were stopped at exactly the same time that the olmesartan was stopped and introduced at the same time that the olmesartan were reintroduced.

I think Occam's razor and general common sense would indicate that the propafenone is what we call a red herring in this case.

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Q. That's your read of the document, but the document is silent on that question of when the propafenone was discontinued; correct?

MR. SLATER: Objection.

MR. MURPHY: Or whether it was discontinued; correct?

MR. SLATER: Objection.

THE WITNESS: The document mentions propafenone but does not make any mention of any change in the propafenone, and so my interpretation is that this was not modulated in perfect congruence with the olmesartan.

Why would someone generate a report where both medicines were stopped at the same time and one is only mentioning one in terms of its starting and stopping and then mentioned as the patient was taking the other medication when, in fact, they were started and

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stopped at the same time? That doesn't seem to make any sense.

I see that propafenone is mentioned and I have no reason to doubt that he had been on propafenone during this time, but I have no evidence to think that someone would only selectively report the dechallenge and rechallenge data regarding olmesartan and totally leave out any relevant propafenone dose changes.

BY MR. MURPHY:

Q. Assuming that they had that information; correct?

A. What I would say is that --

Q. Assuming that they had that information; correct?

A. They of course had information on propafenone, but they did not -- they did not -- the fact that they did not comment on its temporality and the fact that they had access to this

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information indicates to me that they knew about the timing of the olmesartan and they did not see a similar timing with regard to the propafenone.

Q. Does the document that is this MedWatch report indicate what the patient's drug holiday was before rechallenge?

(Pause.)

THE WITNESS: The document indicates when the olmesartan was first stopped and it also indicates that the diarrhea returned when it was restarted. I do not see -- give me a minute. Maybe it's here somewhere.

(Pause.)

THE WITNESS: I do not see a date for the rechallenge; however, rechallenge is mentioned in both the narrative and in the check box. So I can't give you an estimation with regard to the duration of the drug holiday, if

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that's your question.

BY MR. MURPHY:

Q. There's no indication about the duration of the drug holiday; correct?

MR. SLATER: Objection.

You can answer.

THE WITNESS: Certainly one can infer by reviewing this document that there was some degree of drug holiday and that the olmesartan was discontinued and, that at some point afterwards, it was restarted.

It appears that the drug holiday -- well, the length is not specified --

MR. MURPHY: And that was my question.

THE WITNESS: Well, the length is not specified.

It appears that the drug holiday was longer than 12 days and I say that based on the

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narrative that says Benicar was discontinued on January 2nd. The diarrhea and dehydration resolved on January 14th and subsequently in the report -- and elsewhere in the report, rather -- it says that the diarrhea returned when the Benicar was continued, i.e. reintroduced.

I can't give you the precise duration of the drug holiday based on this, but, again, I agree with Allen Feldman. I think that the only plausible cause of this patient's illness was olmesartan enteropathy.

BY MR. MURPHY:

Q. And Dr. Feldman was testifying to what was set forth in the MedWatch report; correct?

A. He, like anyone who interprets MedWatch reports, was applying differential diagnosis and coming to the conclusion that olmesartan was causing

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enteropathy in that scenario.

Q. Is it your testimony, Dr. Lebwohl, that he testified based upon a differential diagnosis that he conducted? Is that your testimony?

A. I don't see him using the words in that -- in that specific instance, but Tina Ho, for example, mentioned that when they're looking at -- and I quote -- when they're looking at the known characteristics of a subject's clinical state, that's differential diagnosis, and later says there's actually definitions of related and not related which, again, just lumps in the different clinical criteria that the medical reviewer would be applying in doing a differential and exercising medical judgment.

And so a differential diagnosis can certainly be applied when reviewing a MedWatch case report.

Q. And my question simply to you is whether you were stating that Dr.

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Feldman conducted a differential diagnosis when he offered his testimony.

A. I do not see him explicitly using the term "differential diagnosis" in that testimony; however, the fact that he mentions that the only plausible cause of this patient's illness was olmesartan indicates that alternative explanations have been considered and rejected.

Q. Let me direct your attention to page 34 of your report.

A. I'm at page 34.

Q. Yes.

And toward the -- I guess four lines up from the bottom of the first paragraph, five actually, you write, "Yasushi Hasebe, the global head of CSPV, based in Japan, was questioned about another adverse event report, and agreed, quote, that the olmesartan was one of the factors causing the severe diarrhea, dehydration, and hospitalization described."

And then you give a cite to

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the deposition and then you state, "These acknowledgments of causality demonstrate CSPV's understanding and acceptance of causality."

A. I see that.

MR. MURPHY: Let me direct your attention to what we'll mark as 15.

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(Deposition Exhibit No. Lebwohl-15, Excerpts from the May 31, 2016 Deposition Transcript of Yasushi Hasebe, was marked for identification.)

- - -

BY MR. MURPHY:

Q. Doctor, I'm handing you what's been marked as Exhibit 15 to your deposition and it is an excerpt from the deposition of Yasushi Hasebe. It includes that section of the deposition that you cite here on page 34. Okay?

A. I'm sorry. I'm looking at page numbers in 160's, 164 --

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Q. Uh-hum.

A. Oh, and I see it skips.

Q. Yeah, I said the excerpt includes what you cite.

A. I see. I'm on page 34. Is there just one page 34?

MR. SLATER: Did you say to go to page 34?

MR. MURPHY: No, I didn't.

THE WITNESS: Oh, I thought you mentioned page 34.

MR. SLATER: That was your report.

MR. MURPHY: No, that was your report.

THE WITNESS: Oh, I was confused. Page 34 of my report, not page 34 of the deposition. A lot of paper.

BY MR. MURPHY:

Q. And on page 34 of your report, you cite to the page of Yasushi Hasebe's deposition where you contend he made an acknowledgment of causality;

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correct?

A. I reference page 173 and, assuming this pagination is the same, let me get there and take a look.

(Pause.)

THE WITNESS: Okay. I'm here.

BY MR. MURPHY:

Q. And on page 173, at line 14, there is questioning by Mr. Slater. Do you see that?

A. I do.

Q. "You're not denying that the olmesartan was one of the factors causing the severe diarrhea, dehydration and hospitalizations described in this adverse event report. You're not denying that, right?"

There was an objection and then Mr. Hasebe says, "Correct, I think that's one of the factors."

Do you see that?

A. I do.

Q. And if you look over on page

174, Mr. Hasebe provides a further explanation. Do you see that? "What I want to say is that if there are other suspect drugs -- as for any other suspect drug, it's one of the combination drugs that are being taken, in those cases then you would have to look into the details, the background of the patient and the various other factors and otherwise you would not be able to identify or make the determination about what causes such symptoms."

Do you see that?

A. I do. I would like to read actually the exchange that happened in between those two excerpts because they were close to each other, and I just want to make sure that I have somewhat of a better context.

MR. SLATER: Are you still going to ask questions about this one or are you done?

MR. MURPHY: No, I'm done.

MR. SLATER: He's done. Let

it go. It's fine.

THE WITNESS: Okay.

MR. SLATER: I'll come back to it on my questioning later.

THE WITNESS: Okay.

MR. SLATER: I promise.

MR. MURPHY: Let me, in the interest of time, ask you to turn to page 36 of your report.

THE WITNESS: I'm on page 36.

BY MR. MURPHY:

Q. And in the first full paragraph, you reference a MedWatch report for an adverse event reported to Daiichi-Sankyo on July 14th, 2005. Do you see that?

A. I see that. I cite it as an example.

(Pause.)

MR. MURPHY: 16.

- - -

(Deposition Exhibit No. Lebwohl-16, Sankyo Post Marketing

Safety Adverse Event Contact Log Attaching 7/19/05 MedWatch Report (Also Marked as Exhibit 129), OLM-DSI-0011876006 through OLM-DSI-0011876014, was marked for identification.)

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MR. SLATER: This whole thing is the exhibit all together?

MR. MURPHY: Yeah.

BY MR. MURPHY:

Q. So, Doctor, you have in front of you Exhibit 16, which is the MedWatch report that you discuss in the first full paragraph on page 36 of your report; correct?

A. I'm just checking to see if the number correlates, 003790. Yes, it does.

Q. And you state in your report that this -- a MedWatch report for an adverse event reported to Daiichi-Sankyo on July 14th, 2005 documents a 36-year-old male who developed severe

vomiting, diarrhea, and weight loss about one year after starting Benicar HCT; correct?

A. Give me a moment just to refresh my memory looking at this MedWatch report again.

Q. I'm just asking whether that's what you say in your report.

A. That's what I write in my report, yeah.

Q. Okay.

(Pause.)

THE WITNESS: Okay. Do you have questions?

MR. MURPHY: Yes, I do.

BY MR. MURPHY:

Q. Again, you indicate that the patient experienced weight loss, severe vomiting, and diarrhea while being treated with Benicar; correct?

A. That's what I wrote.

Q. And, in fact, the patient -- it's reported that the patient started Benicar a year before his symptoms, while

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also intentionally dieting, attempting to lose weight; correct?

A. It does say that he was intentionally dieting; and despite that and even though weight loss is the goal of intentional dieting, the fact that he's reporting weight loss in my opinion doesn't undercut the notion that he's been dieting.

In medicine, we like to say that a successful diet is a disease until proven otherwise. It's very possible that he was trying to lose weight and was unsuccessful and then when he started developing these other severe symptoms, then he was tragically successful in his weight loss or perhaps the weight loss accelerated.

MR. SLATER: One second. He just answered quickly. I just object to the foundation of the question. I didn't want interrupt him. I didn't want to object when he was speaking, but I just wanted

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you to know that because there's a flaw there.

BY MR. MURPHY:

Q. And in this MedWatch form, Exhibit 16 that we're looking at, is there any evidence of a biopsy having been taken?

A. I suspect a biopsy was done --

Q. No, my question is --

A. -- I cannot point you to --

Q. -- it indicated or reflected in the document? That's my question to you.

A. Biopsy, the word, was not used, but there is a pair of important words that strongly suggest a biopsy was done and I believe the biopsy was done in this case. The word is celiac disease. It says concomitant diseases, celiac disease. Celiac disease is triggered by gluten and is diagnosed based on biopsy. The fact that one is going on record with a diagnosis of celiac disease to me

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strongly suggests that a biopsy was done.

In fact, this -- if all I knew was that this was a 35-year-old man with celiac disease, who's black, I would immediately start to wonder about alternative explanations for so-called celiac disease and question if it's a misdiagnosis.

We know that people who self-define as having black race have much less celiac disease in terms of their prevalence; and while it's certainly possible -- and I have a handful of patients with celiac disease who self-identifies African-American -- I also have -- I can remember at least one black patient who was told she had celiac disease, but, in fact, on further workup, had olmesartan enteropathy. And so this to me immediately raises concern. And then -- that's not even seeing that he was on olmesartan yet.

And then I see he was on olmesartan and he had a positive

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rechallenge in the context of two positive dechallenges. This to me is illustrative of the kind of cases that exemplify olmesartan enteropathy.

Q. Doctor, at page 36 of your report --

A. I'm on page 36.

Q. -- at the bottom, toward the bottom of the page, four lines up, you begin a sentence "Another example"? Do you see that?

A. I see it.

Q. "Another example is a MedWatch documenting an adverse event reported to Daiichi Sankyo on September 15, 2005, with regard to a 58 year old female patient who took Benicar for two years."

A. I see that.

MR. MURPHY: I'm going to mark as Exhibit 17 the MedWatch report that you reference.

- - -

(Deposition Exhibit No.

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Lebwohl-17, 9/21/05 E-Mail from Robinson to Risk Management Attaching Two CIOMS, etc. (Also Marked as Exhibit 130), OLM-DSI-0011876015 through OLM-DSI-0011876036, was marked for identification.)

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THE WITNESS: Would you like me to take a look at it and answer some questions?

MR. MURPHY: You can take a look at it now, sure.

(Pause.)

THE WITNESS: There are some duplicate pages here. I'm just going to quickly confirm that there's nothing on one page that isn't on the other, but I think these are exact duplicates.

(Pause.)

THE WITNESS: Okay.

BY MR. MURPHY:

Q. This MedWatch report reports

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on a 58-year-old female; correct? And if you need orientation, you know, look to page -- the Bates page ending in 31.

A. Okay.

Q. I think you have it there in your right hand. I'm talking about the MedWatch report, not your --

A. Because I'm at 36.

Q. Look at the MedWatch report.

A. 31? I don't see page numbers.

Q. That's (Indicating) the page I want you to look at.

A. The one that you're pointing at.

Q. Yes.

A. Okay.

Q. Now, this MedWatch report relates to a 58-year-old female; correct?

A. Yes.

Q. And the patient had complaints of nausea, vomiting, and dehydration; correct?

A. Yes.

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Q. There were no reports or complaints of diarrhea; correct?

MR. SLATER: Objection. You can answer.

THE WITNESS: Give me a moment, please.

I don't see diarrhea mentioned.

BY MR. MURPHY:

Q. The patients who were the subject of the 2012 Rubio-Tapia paper, did they all report diarrhea?

A. Diarrhea, if -- if I recall correctly -- and why don't I take a look to confirm -- diarrhea was an inclusion criterion. So in order to be in the Rubio-Tapia paper, you needed to have diarrhea.

And so it's entirely possible that there were patients even at that time who had olmesartan enteropathy, but didn't make it into the Rubio-Tapia paper because they didn't have diarrhea.

Q. With regard to the patients

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whose charts you reviewed after you spoke with Dr. Green, did those patients all report diarrhea or do you recall?

A. There was a real spectrum. In some people, it was -- diarrhea may have been present, but was less prominent. In others, it was more vomiting, if I recall correctly. I would say that gastrointestinal symptoms globally were a feature, which is how they made their way to us, but I'm not sure if they all had diarrhea.

And certainly it's borne out with the subsequent case reports and case series since the initial Rubio-Tapia paper that no longer we're restricted to requiring diarrhea in order to get into the paper. You can see there's a whole clinical spectrum, including vomiting, which is fairly prominent.

Q. So my question was limited to the charts that you reviewed after having spoken with Dr. Green. You understand that?

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A. In terms of those who I was worried about, I'm not sure they all had diarrhea, if that's what your question is.

Q. So the answer to the question is, you're not sure whether all of those folks had diarrhea?

A. I'm not. It's very possible that they had other gastrointestinal symptoms that were sufficiently distressing to be coming to me and for me to be worrying about them, but diarrhea has clearly not been shown to be present in all patients with olmesartan enteropathy and I don't believe it was present in all of those who we first identified during those revelatory first days.

Q. Is nausea, vomiting, dehydration, in the absence of villous atrophy, sufficient to reach a diagnosis of sprue-like enteropathy?

A. Nausea, vomiting, and dehydration are certainly compatible with

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sprue-like enteropathy related to olmesartan. Now, you still also need to have taken olmesartan. I would say that olmesartan plus those would put it high on my differential. If the patient had never taken olmesartan before, I would not consider olmesartan enteropathy.

Q. Now, did you happen to note in the -- as you reviewed the MedWatch report, that the patient who is being reported here indicated that she did not think that Benicar was the cause of her symptoms?

A. I see that she was quoted on saying that and I also noted at the same time the date at which this happened, which was in 2005, and also I wouldn't have thought back in 2005 that Benicar would be causing this, because almost everyone -- except perhaps internally, almost everyone was in the dark about Benicar and diarrhea. I might have agreed with the patient back then.

Q. But you have no

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understanding or knowledge of why the patient made the statement, assuming it was true that she stated that, that she didn't think the drug had anything to do with her symptoms; you don't know why she stated that, do you?

A. All I know is that she stated that and I might have stated the same thing because, back then, knowledge regarding olmesartan enteropathy was not disseminated, certainly not in the lay public, but even among the very specialists that were seeing these patients.

I think it's important to elicit patients' opinions on what they think is wrong with them. I typically do that in my clinical practice. I think that even though it's an important practice to do, that doesn't necessarily make it true, the statement that the patient says.

Q. In your report, you indicate in at least one point that there were

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certain reports of celiac disease that should have been included in one or more of the Daiichi reports on incidence of celiac disease.

You recall that?

A. I'm going to check my report and look at the specific reference. If you have a page number, I'll be glad to follow your lead.

Q. Okay -- well, let me ask you a slightly different question in the interest of time. You know that there were times when --

A. Oh, I got one if you want.

Q. You got one. Go ahead.

A. So the case that we reviewed recently, the young black man with celiac disease diagnosis, this was one of the reports that I mentioned was not included in the analysis of celiac cases prepared by Herve Caspard. Is that relevant to the question you just asked?

Q. It is, it is.

So when looking for cases of

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celiac disease or any other condition, are you aware that there are search terms that are used to query a database?

A. Generically when looking for any disease and -- in any database?

Q. In an adverse event database.

A. There are certain terms that are queriable and as a general matter of speaking, such terms can be queried, yes.

Q. Have you ever had occasion to generate search terms to query an adverse event database to pull or identify instances of a certain type of adverse event?

A. In general, with regard to any kind of search database or you specifically mean MedWatch reports or you mean in my clinical or research practice?

Q. In your research practice.

A. Have I applied search terms to --

Q. Yes.

A. -- identify adverse events?

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I've certainly employed search terms.

Q. And just so that we're clear, the search terms that you employ, you run them through the database; correct?

A. That's what I meant by employing search terms. I enter them into the database. That's one way to -- it's one way to identify a link, using search terms. I wouldn't say it's necessarily the only way one should try to identify a link.

Q. And if one were looking through an adverse event database for reports suggestive of sprue-like enteropathy or olmesartan-associated enteropathy, they could generate search terms to query an adverse event database; correct?

A. Not if the condition isn't fully characterized or cataloged, for example, like in a registry. So, for example, prior to 2012, when the public was made aware of olmesartan enteropathy,

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it would have been very helpful if Daiichi, for example, had a registry that followed these patients, cataloguing them consistently.

Instead, we're left with scattered reports of celiac disease, likely misdiagnosed as celiac disease, and we have to rely on these secondary endpoints because we don't have a specific term for this disease that was out there, was being reported consistently, but not monitored in a registry or in any other formal capacity.

Q. Do you have any understanding or awareness of how the FDA queries its adverse event database to find reports of a given adverse event?

A. Well, I've never been on the inside of the FDA and had that role, but physically I've been at the FDA and given talks at the FDA. And so I can't say I've looked over the shoulder of someone running these queries --

Q. I'm simply asking you, do

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you know how it's done?

A. I have a general sense how it's done, though if you put me in front of a computer and put an FDA hat on me, I'd probably have trouble getting past the login and password stage, frankly.

Q. And is it your understanding that certain search terms are generated and then input into the database?

MR. SLATER: Objection. We're mixing foundations here.

You can answer.

THE WITNESS: In general when looking for outcomes, various search terms or diagnosis codes are used.

MR. MURPHY: Search terms and diagnosis codes.

THE WITNESS: Yes.

MR. MURPHY: I'm going to mark as Exhibit 18 a list of search terms.

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(Deposition Exhibit No.